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AN 2003:591035 CAPLUS
DN 139:143973
TI 6-Fluorobicyclo[3.1.0]hexane derivatives
IN Nakazato, Atsuro; Chaki, Shigeyuki; Sakagami, Kazunari; Dean, Ryoko; Ohta, Hiroshi; Hirota, Shiho; Yasuhara, Akito
PA Taisho Pharmaceutical Co.,ltd., Japan
SO PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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	EP 1459765	A1	20040922	EP 2002-793421	20021226
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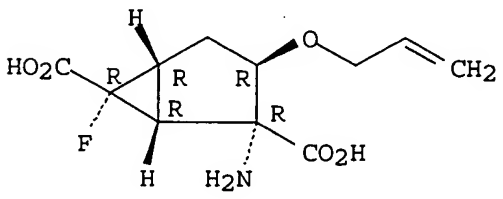
	BR 2002015462	A	20041130	BR 2002-15462	20021226
	US 2005119345	A1	20050602	US 2003-500101	20021226
PRAI	JP 2001-395797	A	20011227		
	WO 2002-JP13693	W	20021226		

OS MARPAT 139:143973
IT **569686-58-4P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(6-Fluorobicyclo[3.1.0]hexane derivs. having group II metabotropic glutamate receptor antagonist actions as antidepressants)
RN 569686-58-4 CAPLUS
CN Bicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 2-amino-6-fluoro-3-(2-propenyloxy)-, (1R,2R,3R,5R,6R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

DERWENT-ACC-NO: 2003-663366

DERWENT-WEEK: 200537

TITLE: 6-Fluorobicyclo(3.1.0)hexane derivatives are group II metabotropic glutamate receptor antagonist useful as antidepressants

INVENTOR: CHAKI, S; DEAN, R ; HIROTA, S ; NAKAZATO, A ; OHTA, H ; SAKAGAMI, K ; YASUHARA, A

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PRIORITY-DATA: 2001JP-0395797 (December 27, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 20050119345 A1	June 2, 2005	N/A	000	A61K 031/195
WO 2003061698 A1	July 31, 2003	J	096	A61K 045/00
AU 2002359923 A1	September 2, 2003	N/A	000	A61K 045/00
EP 1459765 A1	September 22, 2004	E	000	A61K 045/00
KR 2004068348 A	July 30, 2004	N/A	000	A61K 031/196
BR 200215462 A	November 30, 2004	N/A	000	A61K 045/00
JP 2003561641 X	May 19, 2005	N/A	073	C07C 229/50

DESIGNATED-STATES: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG

SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW AT BE BG CH CY CZ DE DK
EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ
TR TZ UG ZM ZW AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV
MC MK NL PT RO SE SI SK TR

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-DATE
US20050119345A1	N/A	2002WO-JP13693	December 26, 2002
US20050119345A1	N/A	2005US-0500101	February 4, 2005
WO2003061698A1	N/A	2002WO-JP13693	December 26, 2002
AU2002359923A1	N/A	2002AU-0359923	December 26, 2002
AU2002359923A1	Based on	WO2003061698	N/A
EP 1459765A1	N/A	2002EP-0793421	December 26, 2002
EP 1459765A1	N/A	2002WO-JP13693	December 26, 2002
EP 1459765A1	Based on	WO2003061698	N/A
KR2004068348A	N/A	2004KR-0710069	June 25, 2004
BR 200215462A	N/A	2002BR-0015462	December 26, 2002
BR 200215462A	N/A	2002WO-JP13693	December 26, 2002
BR 200215462A	Based on	WO2003061698	N/A
JP2003561641X	N/A	2002WO-JP13693	December 26, 2002
JP2003561641X	N/A	2003JP-0561641	December 26, 2002
JP2003561641X	Based on	WO2003061698	N/A

INT-CL (IPC): A61K031/194, A61K031/195 , A61K031/196 , A61K031/1966 ,
A61K031/225 , A61K031/381 , A61K031/3811 , A61K045/00 , A61P009/10 ,
A61P025/00 , A61P025/08 , A61P025/14 , A61P025/16 , A61P025/18 ,
A61P025/188 , A61P025/22 , A61P025/24 , A61P025/28 , A61P025/30 ,
A61P043/00 , A61P043/000 , C07C229/32 , C07C229/50 , C07C229/500
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C07C237/04 , C07C237/24 , C07C255/54 , C07C255/544 , C07D333/16 , C07D333/166

ABSTRACTED-PUB-NO: WO2003061698A

BASIC-ABSTRACT:

NOVELTY - 6-Fluorobicyclo(3.1.0)hexane derivatives (I) and their salts and
hydrates are new.

DETAILED DESCRIPTION - 6-Fluorobicyclo(3.1.0)hexane derivatives of formula (I)
and their salts and hydrates are new.

R1, R2 = H, 1-10C alkoxy, phenoxy, OAlk (optionally substituted by OAlk or 1 or
2 phenyl), 2-6C hydroxyalkoxy, NQQ or NR6CHR7ACOOR8;

Alk = 1-6C alkyl;

Q = H, Alk, AlkOAlk, 2-6C hydroxyalkyl or AlkCOAlk);

R6, R7 = H, Alk (substituted by OH, COOH, phenyl, hydroxyphenyl, naphthyl,
heteroaryl, OAlk, SAlk or CONH2), 2-6C alkyl (substituted by NH2, guanidino or
SH), 1-10C alkyl, phenyl, hydroxyphenyl or naphthyl; or

R6+R7 = CH2, CH2CH2 or (CH2)3;

R8 = H or carboxyl protecting group;

A = bond, CH2, CH2CH2 or (CH2)3;

R3 = 1-10C acyl, 1-6C acyl (substituted by OAlk, COOAlk, or COOH) 2-10C
hydroxyacyl or COCHR7ANHR9;

R9 = H or amino protecting group;

R4, R5 = H, 1-10C alkyl, 2-10C alkenyl, naphthyl 5 membered heteroaryl
containing at least one N or phenyl (optionally substituted by 1-5 halo, 1-10C
alkyl, 1-10C alkoxy, CF3, phenyl, COOH, NH2, NO2, CN or phenoxy); or

R4+R5 = ring.

An INDEPENDENT CLAIM is also included for antidepressants comprising a group II
metabotropic glutamate receptor antagonist.

ACTIVITY - Antidepressant; Tranquilizer, Nootropic; Vasotropic; Neuroprotective; Anticonvulsant; Antiparkinsonian; Cerebroprotective.

MECHANISM OF ACTION - Glutamate-Antagonist.

In assays using CHO cells (1R,2R,3R,5R,6R)-2-amino-3-methoxy-6-fluorobicyc-
lo(3.1.0)hexane-2,6-dicarboxylic acid had an IC50 value for (3H)-MGS00008
binding at glutamate MGluR2 receptors of less than 100 nM (no specific value is
given).

USE - (I) is used as group II metabotropic glutamate receptor antagonists for
treating and preventing depression. (I) may also be useful for treating and
preventing e.g. anxiety, bipolar diseases, Alzheimer's disease, Huntington's
chorea, Parkinson's diseases, amyotrophic lateral sclerosis, ischemia, cerebral
insufficiency, head trauma or spinal cord disorders.

CHOSEN-DRAWING: Dwg.0/2

TITLE-TERMS: HEXANE DERIVATIVE GROUP GLUTAMATE RECEPTOR ANTAGONIST USEFUL
ANTIDEPRESSANT

DERWENT-CLASS: B05

CPI-CODES: B06-H; B07-H; B10-A15; B10-A17; B10-B01; B10-B02; B10-B03; B10-B04;
B10-C02; B10-C03; B10-C04; B10-D01; B10-D03; B14-F02D; B14-J01A1;
B14-J01A3; B14-J01A4; B14-J01B3; B14-J01B4; B14-L06; B14-N16;
B14-N17B; B14-S01;

CHEMICAL-CODES:
Chemical Indexing M2 *01*
Fragmentation Code
G031 G033 G038 G039 G060 G600 H1 H100 H161 H5
H561 H6 H601 H661 H8 J0 J012 J1 J152 M210
M211 M272 M281 M320 M415 M510 M520 M530 M541 M710
M904 M905 P444 P446 P448 P451 P517 P528 P617 P625

P942
Ring Index
00695
Specfic Compounds
ABLD8T ABLD8N

Chemical Indexing M2 *02*
Fragmentation Code
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G012 G013 G019 G020 G021 G029 G031 G033 G038 G039
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H685 H689 H721 H722 H8 J0 J011 J012 J013 J014
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J242 J251 J252 J271 J3 J341 J342 J351 J352 J361
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Ring Index
00695
Markush Compounds
200107-28201-T 200107-28201-N

SECONDARY-ACC-NO:
CPI Secondary Accession Numbers: C2003-180168

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(19) United States

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Nakazato et al. (43) Pub. Date: Jun. 2, 2005

(54) 6-FLUOROBICYCLO[3.1.0]HEXANE DERIVATIVES

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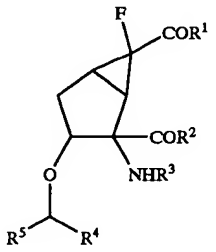
(52) **U.S. Cl.** **514/561**; 562/502

(57) ABSTRACT

An antidepressant comprising, as an active ingredient, a compound having an antagonistic effect on group II metabotropic glutamate receptors, as well as a 2-amino-3-alkoxy-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative of Formula [I]:

[I]



[wherein R^1 and R^2, which may be the same or different, each represent a hydroxyl group, a C_{1-10} alkoxy group, etc.; R^3 represents a C_{1-10} acyl group, a C_{1-6} alkoxy-C_{1-6} acyl group, etc.; and R^4 and R^5, which may be the same or different, each represent a hydrogen atom, a C_{1-10} alkyl group, etc.] or a pharmaceutically acceptable salt or hydrate thereof.

give (1R,2R,3R,5R,6R)-2-amino-3-((R*)-1-(naphthalen-2-yl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester (164 mg) and (1R,2R,3R,5R,6R)-2-amino-3-((S*)-1-(naphthalen-2-yl)-ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester (153 mg), respectively.

[0120] (3) Starting with (1R,2R,3R,5R,6R)-2-amino-3-((R*)-1-(naphthalen-2-yl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester (158 mg) and (1R,2R,3R,5,R6R)-2-amino-3-((S*)-1-(naphthalen-2-yl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester (148 mg), the same procedure as shown in Example 2(3) was repeated to give (1R,2R,3R,5R,6R)-2-amino-3-((R*)-1-(naphthalen-2-yl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (96.0 mg) and (1R,2R,3R,5R,6R)-2-amino-3-((S*)-1-(naphthalen-2-yl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (72.0 mg).

EXAMPLE 4

Synthesis of (1R,2R,3R,5R,6R)-2-amino-3-propyloxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid

[0121] (1) (1R,2R,3R,5R,6R)-2-Amino-3-(2-propenyloxy)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid (40 mg) was dissolved in water (1 mL). To this solution, 10% palladium/ carbon (4 mg) was added and stirred under a hydrogen atmosphere at room temperature for 2 days. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure, followed by addition of tetrahydrofuran (1 mL) and heating at reflux for 1 hour. The reaction mixture was stirred at room temperature for an additional 3 hours, filtered to remove any solids, and then purified on an ion-exchange resin (AG 50W-X8 Resin (H-type), developing solvent: water, 50% aqueous tetrahydrofuran, 10% aqueous pyridine) to give (1R,2R,3R,5R,6R)-2-amino-3-propyloxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (30 mg).

EXAMPLE 5

Synthesis of (1R,2R,3R,5R,6R)-2-amino-3-cyclopentyloxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid

[0122] (1) Starting with crude 2-cyclopentenyl-2,2,2-trichloro-acetimidate (375 mg) prepared from 2-cyclopenten-1-ol and (1R,2R,3R,5R,6R)-2-azide-3-hydroxy-6-fluorobicyclo[3.1.0)-hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester (650 mg), the same procedure as shown in Example 2(1) was repeated to give (1R,2R,3R,5R,6R)-2-azide-3-(2-cyclopentenyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester (339 mg).

[0123] ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm); 1.32 (3 H, t, J=7.3 Hz), 1.90-2.52 (8 H, m), 3.94-4.14 (1 H, m), 4.27 (2 H, q, J=7.3 Hz), 4.52-4.79 (1 H, m), 5.15-5.41 (2 H, m), 5.58-5.82 (1 H, m), 5.88-6.04 (1 H, m), 7.30-7.46 (5 H, m).

[0124] MS(ESI)(Pos)m/z; 452 $(M+Na)^+$

[0125] (2) (1R,2R,3R,5R,6R)-2-Azide-3-(2-cyclopentenyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester (331 mg) was dissolved in acetic acid (18 mL) and water (6 mL). To this solution, 10% palladium/carbon (39 mg) was added and stirred under a hydrogen atmosphere at room temperature for 24 hours. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in tetrahydrofuran (7.36 mL) and water (3.53 mL), followed by addition of lithium hydroxide hydrate (80 mg) and stirring at room temperature for 4 hours. After the solvent was distilled off under reduced pressure, the resulting residue was purified on an ion-exchange resin (AG 50W-X8 Resin (H-type), developing solvent: water, 50% aqueous tetrahydrofuran, 10% aqueous pyridine) to give (1R,2R,3R,5R,6R)-2-amino-3-cyclopentyloxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (61 mg).

EXAMPLE 6

Synthesis of (1R,2R,3R,5R,6R)-2-amino-3-(3-nitrobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester, (1R,2R,3R,5R,6R)-2-amino-3-(3-aminobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester and (1R,2R,3R,5R,6R)-2-amino-3-(3-aminobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid

[0126] (1) Starting with crude 3-nitrobenzyl-2,2,2-trichloro-acetimidate (562 mg) prepared from 3-nitrobenzyl alcohol and (1R,2R,3R,5R,6R)-2-azide-3-hydroxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester (380 mg), the same procedure as shown in Example 2(1) was repeated to give (1R,2R,3R,5R,6R)-2-azide-3-(3-nitrobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester (279 mg).

[0127] ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm); 1.32 (3 H, t, J=7.2 Hz), 1.34 (3 H, t, J=7.2 Hz), 2.22-2.42 (2 H, m), 2.50 (2 H, dd, J=2.7, 7.8 Hz), 3.94-4.10 (1 H, m), 4.20-4.46 (4 H, m), 4.58 (1 H, d, J=12.1 Hz), 4.80 (1 H, d, J=12.1 Hz) 7.44-7.66 (2 H, m), 8.03-8.24 (2 H, m).

[0128] MS(ESI)(Pos)m/z; 459 $(M+Na)^+$

[0129] (2) Starting with (1R,2R,3R,5R,6R)-2-azide-3-(3-nitro-benzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester (275 mg), the same procedure as shown in Example 2(2) was repeated to give (1R,2R,3R,5R,6R)-2-amino-3-(3-nitrobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester (120 mg).

[0130] (3) (1R,2R,3R,5R,6R)-2-Amino-3-(3-nitrobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester (120 mg) was dissolved in acetic acid (0.21 mL). To this solution, zinc powder (101 mg) was added and stirred at room temperature for 3 hours. The reaction mixture was filtered to remove any solids, followed by addition of ice-cold saturated sodium bicarbonate. After the reaction mixture was extracted twice with ethyl acetate, the combined organic layers were washed with 0.5 M aqueous sodium carbonate and saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate. After the drying agent was filtered off, the filtrate was concentrated under reduced pressure and the resulting residue was purified by column chromatography (silica gel: Wako gel C200, developing solvent: chloroform/ethanol=30/1) to give (1R,2R,3R,5R,6R)-2-amino-3-(3-aminobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester (96 mg).